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Preface

Molecular basis of disease: Arterial hypertension

Human arterial hypertension is a complex, multifactorial quantitative trait under polygenic control. Candidate genes involved in primary arterial hypertension have been identified in the last 20 years. They are mostly implicated in mechanisms of sodium metabolism and its regulation. Long-term excess of dietary sodium has been known for a long time to cause arterial hypertension. The body's sodium accumulation causes water retention in order to maintain physiological osmolarity of bodily fluids and cellular volume. Interestingly, some recent findings indicate that intracellular osmolarity is sensed by protein kinases measuring intracellular concentrations of Na^+ and Cl^- such as SIK1 and WNK kinases. They may modulate active sodium transport and cause numerous hormonal responses.

The body's control of Na^+ metabolism is achieved mainly by the kidney, and hence the number of nephrons of an individual as control units of sodium metabolism as well as proteins and hormones regulating renal transepithelial Na^+ and fluid metabolism are important regulatory criteria. Recent analysis of various monogenic forms of essential hypertension led to a more fundamental understanding of the disease by the identification of proteins and their hormonal control systems involved in renal Na^+ metabolism. Evidently, not only mutations of the apical renal tubular Na^+ channels (EnaC) and of the proteins of the intracellular hormone signaling machinery may lead to hypertension, but also defects of intracellular trafficking and turnover of the proteins. More recently, the important role of the basolaterally located renal sodium pumps in regulating the transepithelial tubular Na^+ transport of kidneys has come into the focus of research. In particular, the discovery of endogenous cardiac glycosides as new steroid hormones that induce hypertension and use the sodium pump as a hormone receptor sheds a new light on the disease. This cardiotonic steroid hormone system is intimately linked to the renin–angiotensin–aldosterone and adrenergic systems. An unexpected discovery was the finding that the cardiac glycoside receptor site acts as a signal transducer at concentrations of endogenous cardiac glycosides that are not inhibitory toward the sodium pump. This transducing and signaling system is interlinked with other blood pressure-regulating hormonal systems. Defects in the internalization of the cardiac glycoside receptor by a defective renal cytoskeleton due to a mutation of the cytoskeletal protein adducin were discovered to be a cause of monogenetic hypertension, showing again that alterations of trafficking of membrane proteins are important. The successful search for ouabain antagonists to treat hypertension may have opened up a new principle of antihypertensive therapy.

This collection of reviews by leading scientists in the field reports on the signal transduction mechanisms of blood pressure-regulating hormones and how alterations lead to vascular contraction and, as a consequence of the ensuing hypertension, to an alteration of the function of endothelial cells, effects on nutritional transport through the placenta, loss of function of renal glomeruli, remodeling of the heart, and an altered hormonal control system of Na^+ metabolism in the brain.

I am most grateful to all the contributors and reviewers for their efforts in making this special issue a reality. My sincere thanks to the BBA staff for my endowment with this task to assemble reviews from leading laboratories in this special issue and to Jeff Rossetti for his professional support during the task.

Wilhelm Schoner
Institute of Biochemistry and Endocrinology,
Justus-Liebig-University Giessen, Frankfurter Str. 100,
D-35392 Giessen, Germany
E-mail address: wilhelm.schoner@vetmed.uni-giessen.de.

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Dr. Wilhelm Schoner is Professor Emeritus of Biochemistry at the Institute of Biochemistry and Endocrinology of the Justus-Liebig-University Giessen. He studied medicine, receiving his medical degree on 1962 at the Johannes-Gutenberg-University of Mainz. This was followed by seven years of training in biochemistry at the universities of Frankfurt/M and Göttingen, where he obtained his habilitation in biochemistry in 1969. From 1972 to 2003 he was professor and chairman of the above institute in Giessen. His research focused on the mechanism of the sodium pump, and by the use of fluorescent and substitution-inert Mg-ATP analogs, he was able to conclude that sodium pumping needs the cooperation of catalytic α subunits in this process. In investigating the biological role of cardiac glycosides as specific inhibitors of the sodium pump, he isolated ouabain from bovine adrenal glands and verified its structure. Moreover, he realized that blood levels of endogenous ouabain can become elevated within minutes upon physical exercise and also drops rapidly upon rest, thus supporting the concept that a compound heretofore only recognized as a plant toxin can act as an endogenous mammalian steroid hormone regulating blood pressure and heart function.

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